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TITLE PAGE

Sesame Allergy In Adults: Investigation And Outcomes Of Oral Food Challenges

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Sesame (*Sesamum indicum*) allergy is the most common seed allergy and has been increasingly reported worldwide (1). The variation in prevalence between populations is likely due to different food habits and awareness. Similar to peanut, IgE-mediated sesame allergy begins early in life (usually before 2 years) and persists in 80% of patients (2). Clinical manifestations range from mucocutaneous, respiratory and gastrointestinal manifestations to life-threatening systemic anaphylaxis. Accurate diagnosis of sesame allergy is therefore crucial but the value of skin prick tests (SPT) and sesame-specific IgE (sIgE) have been questioned. Previous studies, largely performed in children, suggest that neither tests sufficiently predict true allergy as determined by oral food challenges (OFC) (3-5). This is of particular concern as anaphylaxis in adult patients with both negative SPTs and sIgE have been reported (3). We performed a retrospective evaluation of the utility of SPT, sIgE and other clinical parameters in predicting sesame allergy confirmed by OFC in adults.

We reviewed the clinical data of all patients who had undergone sesame OFC at Guy's & St. Thomas' and Royal Brompton & Harefield NHS Foundation Trusts, (London, United Kingdom) between 2010 and 2016. SPT were performed with a variety of sesame-containing products including a commercially available solution (Allergopharma, Germany), or prick-to-prick testing with sesame seeds, Sesame Snaps (Anglo-Dal Ltd, UK), sesame oil, halva and/or tahini. When multiple reagents for SPT were used, the result with the largest wheal diameter was used for analyses. sIgE to sesame seed antibody was performed with the ImmunoCAP system (Phadia, Sweden). All patients underwent OFC with sesame seeds, Sesame Snaps, sesame oil or tahini. The starting dose, subsequent increments, interval times and a decision to obtain intravenous access were individualized for each patient after a clinical assessment. Severity of reactions was retrospectively graded from the clinical records according to Ring and Messmer's classification

(6). Association analysis with the Fisher's exact test and independent samples t-test were used to compare categorical and continuous variables between sesame allergic/non-allergic patients respectively.

Over the 6-year study period, records were available for 33 patients who underwent supervised sesame OFC. Overall, the median age was 32 (range: 16-81) years and the male:female ratio was 1:2. Sixteen (48%), 12 (36%), and 10 (30%) patients had history of allergic rhinitis, asthma and atopic dermatitis respectively. Twenty-one patients (64%) had a suggestive history of reactions after exposure to sesame-containing foods, while the remainder did not have a clear or previous exposure to sesame. Eleven patients (33%) had positive SPT, defined as wheal diameter ≥ 3 mm; 13 patients (39%) had positive sIgE, defined as ≥ 0.35 kUA/l; and 9 (27%) patients had both positive SPT and sIgE. There were 10 (30%) positive challenges and further information is summarized in Table 1. Half of patients (5/10) with positive OFC had reactions of grade ≥ 3 in severity either during their index reaction or OFC. Two serious reactions (patients #1 and #4) required 2 doses of intramuscular adrenaline for refractory hypotension.

Association analyses showed no significant differences in age ($p=0.41$); gender ($p=0.24$); history of reaction to sesame ($p=0.26$), atopy (allergic rhinitis [$p=0.06$], asthma [$p=0.06$], atopic dermatitis [$p=0.12$]), other food allergies ($p=0.06$) or mean SPT diameters ($p=0.06$) and sIgE values ($p=0.25$) between patients with positive and negative OFC. Moreover, the absolute mean SPT wheal diameters and sIgE values were smaller in the positive (0.3 ± 1.0 mm, 0.16 ± 0.29 kUA/l) than negative OFC group (1.4 ± 1.6 mm, 2.00 ± 4.85 kUA/l). In this selected cohort, SPT had a

sensitivity of 10.0% and specificity of 56.5% (diameter ≥ 3 mm as cut-off); and sIgE had a sensitivity of 10.0% and specificity of 42.9% (≥ 0.35 kUA/l as cut-off).

To the best of our knowledge, we present the largest cohort of sesame challenges performed in adults. There were no significant differences in SPT, sIgE results or studied clinical parameters between allergic and non-allergic patients. Out of 10 positive OFC, 9 (90%) had both undetectable sIgE and negative SPT despite using a variety of different sesame sources, highlighting the poor discriminative value of these tests and the importance of OFC. We recommend sesame OFC in cases with a suggestive clinical history but negative SPT/IgE testing and only after evaluation of risk/benefits for each individual patient. We also advise cautious graded protocols and consideration of prophylactic cannulation.

The poor sensitivity of sesame tests may be due to a lack of clinically relevant allergens in testing agents. Leduc *et al.* identified hydrophobic oleosins (Ses i 4 and Ses i 5) as major sesame allergens and sensitization to oleosins seem to be associated with more severe systemic reactions (2). The poor performance of SPT with commercial extracts may be attributed to the paucity of oleosins. Analogous to peanuts, the roasting process may increase the allergenicity of sesame proteins and tahini (a toasted oil-based sesame seed paste) might therefore represent an alternative agent for SPT (7). However, we did not find tahini to confer any additional value compared to other sesame sources, with all 7 patients tested with tahini in the positive OFC group having negative SPT results.

Various sesame preparations are available for OFC and no evidence for superiority of any one form. From our experience, we recommend Sesame Snaps as a palatable and convenient

preparation which has reliably lead to positive challenges. The utility of additional investigations such as basophil activation tests, “contact test” with sesame oil, and component-resolved diagnosis with Ses i 1 warrant further investigation (8-10).

Our study is limited by its retrospective nature and non-standardized use of various sesame sources for SPT and OFC. Using the largest value for SPT (when multiple results were available) for analysis may lead to under-estimation of specificity.

In conclusion, our study adds to previous reports and confirms that SPT and sIgE results are not predictive of sesame allergy in adults. No studied clinical parameters were different between allergic and non-allergic patients. OFC remains essential for diagnosis, but should be conducted cautiously under experienced supervision due to the inherent severity and unpredictability of sesame reactions. Further work to improve the diagnostic accuracy of skin and serum testing is needed.

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Table 1 – Clinical summaries of 10 patients with positive oral food challenges

#	Sex /age	Grade	Index reaction	Atopy; other food allergies	SPT wheal diameter (source)*	sIgE, kUA/l	Cumulative dose	OFC Reaction	Treatment
1	F/30	1	Rash over hands/face, loss of consciousness	Nil; nil	0mm (solution)	<0.35	6.5g (seed)	Perioral tingling, palpitations, flushing, hypotension (SBP 70mmHg)	2 doses of IM Adrenaline, IV anti-histamines and corticosteroids.
2	F/39	2	Tongue swelling with throat constriction, generalised urticaria	Nil; nil	0mm (solution, seed, tahini)	<0.35	1.75g (Sesame Snaps)	Urticaria	IV anti-histamines and corticosteroids
3	M/43	2	Neck rash, abdominal pain, generalized swelling, throat tightness, dyspnoea	Nil; nil	0mm (solution, oil, sesame snaps, halva)	<0.35	6.6g (Sesame Snaps)	Urticaria, flushing	Oral anti-histamines and corticosteroids
4	M/16	3	Sesame naïve, history of contact rash in infancy	Allergic rhinitis, asthma, atopic dermatitis; peanut and egg	3mm (solution)	0.91	6.5g (Sesame Snaps)	Urticaria, facial angioedema, hypotension (SBP 60mmHg)	2 doses of IM Adrenaline, IV anti-histamines and corticosteroids
5	F/16	3	Urticaria, facial swelling	Nil; nil	0mm (solution, oil, seed, tahini)	<0.35	1ml (sesame oil)	Palmar erythema, pruritus, coughing with wheeze on auscultation (PEFR 480 → 360l/min)	Salbutamol nebuliser, oral anti-histamines and corticosteroids
6	F/27	3	Flushing, pruritus, diarrhoea (after non-specific foods)	Nil; soy	0mm (seed, tahini)	<0.35	¼ tablespoon (tahini)	Urticaria, abdominal pain	-
7	F/35	3	Facial swelling, throat tightness, hypotension	Nil; nil	0mm (seed, oil, tahini)	<0.35	5ml (tahini)	Urticaria	-
8	M/50	2	Generalized pruritus, lip swelling, throat tightness	Nil; nil	0mm (tahini)	<0.35	0.25ml (tahini)	Urticaria	Oral anti-histamines
9	M/54	3	Facial swelling, dyspnoea, feeling faint	Allergic rhinitis; nil	0mm (seed, oil, tahini, oil skin test)	<0.35	1ml (tahini)	Urticaria, periorbital angioedema	Oral anti-histamines and oral steroids
10	M/32	1	Flushing, facial swelling	Nil; nil	0mm (seed, tahini)	<0.35	5ml (tahini)	Urticaria, flushing	Oral anti-histamines

* SPT values (with exception to patient #4) for all tested allergens were all 0mm